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Research Article

Evaluation of the anticonvulsant, hypnotic and anxiolytic-like effects of methanol seed extract of *Dennettia tripetala* in mice

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ABSTRACT

Background: Epilepsy is a chronic neurological disease characterized by recurrent seizure together with sleep disorder and anxiety. Current drugs used in the management of this disease conditionare associated with serious side effects, relapse and ineffectiveness in wide population necessitating the search for alternative therapy. The fruit of *Dennettia tripetala* (DT) is widely used for its various health-promoting effects including relief of seizures, insomnia and anxiety in ethno-medicine. Hence, this study investigated the effects of methanol seed extract of DT on convulsion, hypnosis and anxiety in mice. **Methods:** Convulsion was induced *with intraperitoneal injection of* pentylenetetrazole (PTZ) (80 mg/kg) 60min *after oral pretreatment of mice with DT (*61.25, 122.5 and 245 *mg/kg), diazepam (2 mg/kg) or distilled water (10 mL/kg).* T*he animals were then observed* for 30min for the occurrence of seizure. *Interaction study with flumazenil on the anticonvulsant effect of DT was assessed.* The effects of *DT (*61.25, 122.5 and 245 *mg/kg, p.o.)* on hypnosis and anxiety were also evaluated using pentobarbital-induced hypnosis and elevated-plus maze tests in naïve mice. **Results:** *DT (*61.25, 122.5 and 245 *mg/kg)* significantly prevented PTZ-induced convulsion relative to control; however, *flumazenil reduced the anticonvulsant effect of DT.* Pretreatment with DT produced anxiolytic-like effect in naïve mice, reduced sleep-latency and enhanced total-sleeping time in pentobarbitone-treated mice. **Conclusions:** The results of this study suggest that the seed extract of *Dennettia tripetala* possesses anticonvulsant, hypnotic and anxiolytic-like properties. The positive effects of DT may be related to central enhancement of GABAergic activity.

INTRODUCTION

Epilepsy is a chronic debilitating neurological disease characterized by unpredictable, recurrent seizure due to abnormal brain rhythmicity (Hingray et al., 2019). It is one of the most common neurological disorders that affect over 70 million individuals of all ages across the globe (Ngugi et al., 2010, 2013). Public misunderstanding of the disease cause serious neurological challenges that are often more severe than the seizures, and this has precipitated other health conditions such as anxiety, sleeplessness, and depression (Ngugi et al., 2013). Notably, brain injury, trauma at birth, infections, poor access to good health care, socioeconomic stress, false perception and attitudes about causes and consequences of epilepsy have implication in the high prevalence of the disease in Africa (Ngugi et al., 2013), notably Nigeria (Ekehand Ekrikpo, 2015). Moreover, the misconception, stigma and inferiority complex attached to epilepsy in Africa have been reported to negatively affect the sleep pattern and also contribute to increased anxiety (Baskind and Birbeck, 2005; Ngugi et al., 2013; Ekeh and Ekrikpo, 2015). Various reports have identified a classical association between seizure, sleep deprivation and anxiety in patients with epilepsy (Dinner and Luders, 2001; Kataria and Vaughn, 2016; Pham et al., 2017). Thus, insomnia and anxiety are prominent phenotypes of epilepsy and both have been implicated as contributory factors responsible for the poor quality of life of patients with epilepsy (Kataria and Vaughn, 2016; Hingray et al., 2019).

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Although the bidirectional pathophysiological relationship between anxiety, insomnia and epilepsy is unknown, altered interplay between inhibitory and excitatory neuronal activity plays integral roles in the pathogenesis of epileptic disorders (Aroniadou-Anderjaskaet al., 2008; Yin et al., 2013). It is recognized that neuronal hyper-excitability in epileptic brain is due to an imbalance between glutamate-induced excitation and gamma-amino butyric acid (GABA)-mediated inhibition(Yin et al., 2013; Hingray et al., 2019). Indeed, deficits in GABA-mediated signaling and hyperactivity of glutamatergic transmission have been documented in various types of epilepsy and also form the basis for the treatment of the disease (Aroniadou-Anderjaskaet al., 2008). However, it is believed that management of epilepsy is not only about treating seizure, but also involves correcting associated neurological diseases such as sleep disorder and anxiety in order to maximize the quality of life of persons with epilepsy (Hingray et al., 2019). It has been reported that current drugs used in the management of convulsion and anxiety are ineffective and highly associated with serious adverse effects in large number of patients (Chin, 2012; Manchishi, 2018). Moreover, previous clinical and ethno-medicinal surveys have also reported that large number of persons with epilepsy in developing countries do not get proper medical care hence resort to the use of herbal products from traditional medical practitioners (White, 1997; Chin, 2012; Manchishi, 2018).

Dennettia tripetala, commonly known as pepper fruit, is a tropical rain forest plant belonging to the family of annonacaea and widely grown in some parts of West Africa including Nigeria (Enwere, 1998).*Dennettia tripetala* has been used as food preservative and seasoning agents and thus the seeds are consumed as condiments because of the spicy and peppery zesty nature (Okafor, 1980). Ethno-medicinal survey showed that *D. tripetala* is used as a remedy for anxiety, pain, amnesia, convulsions, diabetes, typhoid, cough and fever (Okafor, 1980). The fruits are also applied to foods of pregnant women and diets of postpartum women, for which spices and herbs are claimed to aid uterine contraction (Okafor, 1980; Enwere, 1998).The health benefits of *D. tripetala*fruits have been ascribed to the presence of essential *phytochemical constituents such as* alkaloidal compounds (uvariopsine, Stephan thrine, argintinine), vanillin, tannins, steroids, flavonoids, cardiac glycosides, saponins, and terpenoids as well as antioxidants like vitamins A, C and E (Adeotiet al., 2000; Elekwa et al., 2011); most of which have been shown to demonstrate beneficial effects to human health (Sparg et al., 2004). Previous studies have shown that the fruit and seed extracts of *D. tripetala* possess anti-oxidant (Okolie et al., 2014), anti-inflammatory, anti-nociceptive (Oyemitan et al., 2008), memory enhancing (Oyemitan et al., 2019), anti-diabetic (Anioke et al., 2017), renoprotective (Anioke et al., 2017), anti-cancer (Jagla, 2013) and anti-ulcerogenic (Bright et al., 2017) activities. However, most of these studies focused on the essential oils of the fruit whereas the whole fruit extract, which represents the commonest preparation used in traditional medicine (Sofowora, 1993) has not been extensively studied pharmacologically. Hence, this present study is aimed at investigating the effects of methanol seed extract of *D. tripetala* (DT) on convulsions induced by pentylenetetrazole in mice. The sleep promoting and anxiolytic-like effects were also evaluated.

METHODS

Collection and Identification of the Plant Materials

The *Dennettia tripetala* G.Baker (Annonaceae) was collected from a local market in Port Harcourt, the Rivers state, Nigeria. The authentication of the plant and taxonomical identification was done by Dr. Ekeke Chimezie at the herbarium section of the Department of Botany, Faculty of Science, University of Port Harcourt, Nigeria. A voucher specimen with number UPH/C/069 was deposited at the herbarium, Department of Botany, Faculty of Science, University of Port Harcourt.

Preparation of seed extract of D. tripetala

The fresh fruits were allowed to ripe at room temperature; seeds were removed, chopped into pieces and dried at room temperature. Thereafter, the dried seeds were pulverized into powder using electric blender. The powdered dried seed material (600 g) was soaked in methanol for 72 h. The solution was then filtered using Whitman 3 mm thick filter paper. The filtrate was concentrated using a rotary evaporator at 40°C and the 7.34% yield obtained was dried in a desiccator before it was kept in a sterilized glass vial ready for use. The residue was dissolved in normal saline immediately before use.

Experimental animals

Male Swiss albino mice (20-25 g) were used in this study. They were obtained from the animal house, Department of Pharmacology, Faculty of Basic Medical Sciences, University of Port Harcourt, Rivers State. The animals were kept in the laboratory under standard conditions, fed with standard animal feeds prior to, and throughout the period of experimentation with 12:12 hr dark and light cycle. The experimental procedures were carried out in accordance with the Research Ethics Committee (UPH/CEREMAD/REC/04) of the University of Port Harcourt in strict compliance with the

National Institutes of Health (NIH) Guideline for the Care and Use of Laboratory Animals.

Drugs and Chemicals

Pentylenetetrazole – PTZ was obtained from Sigma, USA. Pentobarbital - PB and diazepam – DP were purchased from a Pharmacy store in Port Harcourt, Rivers State, Nigeria. Drugs were dissolved in distilled water immediately before use.

Acute toxicity test

The method described by Lorke (1983) was used to determine the median lethal dose (LD_{50}) of the methanol seed extract of *Dennettia tripetala*,as an index of acute toxicity. Treated animals were monitored for signs of toxicity and mortality for 24 h. The LD_{50} was then calculated as the geometric mean of the highest dose showing no death and the lowest dose showing death. The doses of 61.25, 122.5 and 245 mg/kg of *D. tripetala* used in the study were chosen as $1/10^{th}$, $1/20^{th}$, and $1/40^{th}$ of the LD_{50} value obtained and also based on preliminary studies.

Phytochemical screening of the methanol seed extract of Dennettia tripetala

The medicinal properties of plants are due to varieties of secondary metabolites such as alkaloids, flavonoids, tannins and terpenoids. Accordingly, phytochemical screening tests were carried out on the methanol seed extract using standard procedures to identify the constituents as previously described (Ajayi et al., 2017).

Experimental procedures

Effect of methanol seed extract of Dennettia tripetala on pentobarbital-induced hypnosis

The effect of DT on pentobarbital-induced hypnosis was assessed according to previously described method (Rakhshandeh et al., 2012), which is based on the prolongation of pentobarbital-induced sleeping time. Mice were culled into 5 treatment groups (n = 6). Group 1 which served as normal control received normal saline (NS) (10 mL/kg, p.o.), groups 2-4 were pretreated orally with DT (61.25, 122.5 and 245 mg/kg), while group 5 was given diazepam (2 mg/kg) 60 min prior to induction of sleep with intraperitoneal injection of pentobarbital (50 mg/kg). Thereafter, the onset of sleep for each mouse, which is the time the animals remained immobile and lost their righting reflex, was recorded. Meanwhile, the time interval between the injection of pentobarbital and the onset of sleep was considered as the sleep latency (Rakhshandeh et al., 2012). Each animal was observed for 2 h; hence any animal that failed to sleep within the period was assigned the maximum sleep latency of 120 min and 0 min corresponding sleeping time.

Effect of methanol seed extract of Dennettia tripetala on elevated plus maze test

The effect of DT on elevated plus maze test as an index of anxiolytic activity was carried out according to the method of Pellow et al., (1985). The apparatus consists of a central square platform (5 x 5 cm) from which emanated two open arms (30 x 5 x 0.25 cm) and two closed arms (30 x 5 x 15 cm) directly opposite each other, respectively. The entire apparatus is elevated to a height of 50 cm above floor level. Animals were divided into five treatment groups (n = 6). Mice in group 1 received vehicle (normal saline; 10 mL/kg, p.o.), groups 2-4 were pretreated with DT (61.25, 122.5 and 245 mg/kg, p.o.) while group 5 received diazepam (2 mg/kg, p.o.) as the reference drug. Sixty minutes later, the mouse was placed at the edge of an open arm, with its head facing the center and allowed to explore the maze for 5 min. During the test period, the following measurements were recorded: the total number of arm entries and the time spent in open and closed arms. An entry with all feet put into one arm is defined as an arm entry in this experiment. Ethanol (70%) was used to clean the maze after each test session to prevent residual odor bias (Pellow et al., 1985).

Effect of methanol seed extract of Dennettia tripetala on convulsions induced by pentylenetetrazole

The effect of DT on PTZ-induced convulsions was evaluated according to the method described by Kendall et al., (1981). Mice (n = 6) were pretreated by oral administration of DT (61.25, 122.5 and 245mg/kg), diazepam (2 mg/kg) or vehicle (*saline,* 10 mL/kg) 60 min prior to induction of convulsions with i.p, injection of PTZ (80 mg/kg). The animals were then observed individually in a transparent chamber for the appearance of convulsions or latency to convulsions for a period of 30 min after administration of PTZ.

Involvement of GABAergic system in the activity of Dennettia tripetala in mice

In order to investigate the possible involvement of GABAergic neurotransmission in the anti-convulsant-like activity of DT in the pentyenetetrazole-induced convulsion, the animals were pretreated with flumazenil (2 mg/kg, i.p., a $GABA_A$ receptor antagonist) 15 min prior to administration of DT (122.5 mg/kg, p.o.) or diazepam (2 mg/kg, p.o.). Sixty min later, PTZ (80 mg/kg,i.p.) was administered, and the incident of convulsions, percentage protection (ratio of survival) and percentage mortality (ratio of deaths) were recorded.

However, animals that survived beyond 30 min after injection of PTZ were regarded as being protected (Ayoke et al., 2006).

Statistical analysis

The data obtained were expressed as mean ± S.E.M (standard error of mean) and analyzed with Graph Pad Prism software version 5.00. Statistical analysis of data was done using One-way ANOVA, followed by Bonferroni post-hoc test. P-values less than 0.05 (p<0.05) were considered statistically significant.

RESULTS

Phytochemical analysis of methanol seed extract of D.tripetala

The result of phytochemical analysis of methanol seed extract of *D.tripetala* is shown in Table 1. Phytochemical screening of the methanol seed extract revealed that DT contains alkaloid, tannis, cardiac glycosides, flavonoids, saponin glycosides, carbohydrates and steroids in significant amounts (Table 1).

Table 1: Phytochemical analysis of methanol seed extract of D.tripetala

Phytochemical	Results
Alkaloid	+
Tannins	+
Cardiac glycoside	+
Flavonoids	+
Carbohydrates	+
Sarponin glycoside	+
Steroid	+

+ = Present

Effect of Dennetia tripetala on pentobarbital-induced hypnosis in mice

The effect of DT methanol seed extracton sedation using pentobarbital-induced hypnosis test is presented in Fig. 1A-B. Pretreatment with DT (61.25, 122.5 and 245 mg/kg, p.o) or DP (2 mg/kg, p.o.) significantly (p <0.05) potentiated pentobarbital-induced hypnosis as evidenced by decreased sleep latency relative to control (Fig 1A). However, treatment with higher dose of DT (245 mg/kg, p.o.) and DP (2 mg/kg, p.o.) significantly (p <0.05) enhanced the sleeping time when compared with control group (Fig. 1B).

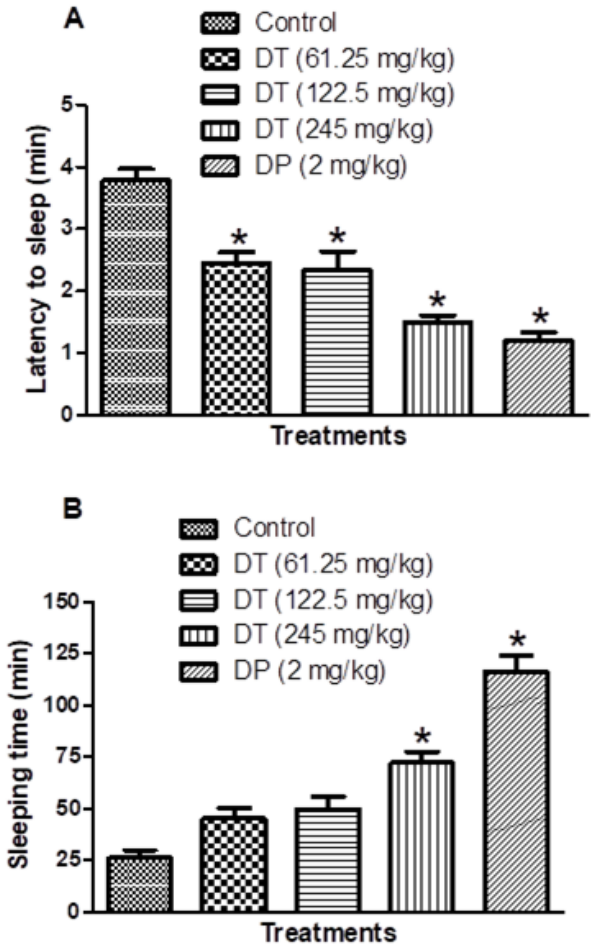

Fig. 1: Effect of *methanol seed extract of Dennetia tripetala* on pentobarbital-induced hypnosis: A) latency to sleep and B) sleeping time in mice. Each bar represents the mean ± S.E.M of 6 animals/group. *p < 0.05 as compared with control (one-way ANOVA followed by Bonferonni*post hoc* test).

Effect of methanol seed extract of Dennetia tripetala on elevated-plus maze in mice

The effect of methanol seed extract ofDT on the elevated-plus maze is shown in Fig 2A-D. Treatment with higher doses of DT (122.5 and 245 mg/kg, p.o) and DP (2 mg/kg, p.o.) significantly (p <0.05) increased the duration of time spent in the open arm (Fig 2A) and decreased the duration of time spent in the closed arm (Fig 2B) when compared with control groups respectively. Also, similar to DP (2 mg/kg, p.o.), DT (122.5 and 245 mg/kg, p.o) demonstrated significant (p <0.05) increase in the frequency visits to the open arm (Fig 2C) but decreased the number of entries into the closed arm (Fig 2D) when compared with control groups suggesting anxiolytic-like effect. However, treatment with lower dose of DT (61.25 mg/kg. p.o.) did not produce anxiolytic-like effect in the elevated-plus maze compared to control group.

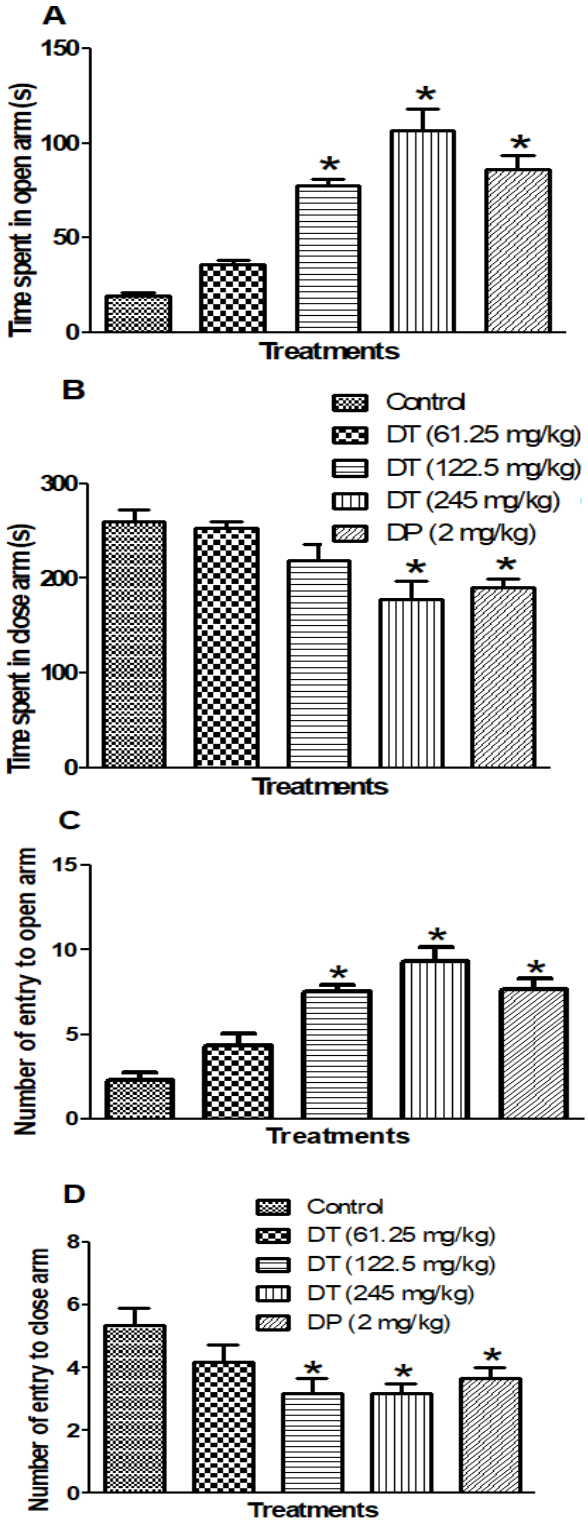

Figure 2: *Effect of methanol seed extract of Dennetia tripetala on elevated-plus maze in mice*: (A) Duration of time spent in the open arm, (B) Duration of time spent in the closed arm, (C) Number of open arm entries, and (D) Number of close arm entries in the elevated-plus maze. Each bar represents the mean ± S.E.M of 6 animals/group. *$p < 0.05$ as compared with control (one-way ANOVA followed by Bonferonni*post hoc* test).

Effect of methanol seed extract of Dennetia tripetala on pentyenetetrazole-induced convulsions

As presented in Table 2,DT (122.5 and 245 mg/kg, p.o) or DP (2 mg/kg, p.o.) significantly (p <0.05) inhibits PTZ (80 mg/kg, i.p.)-induced convulsion in mice as indicated by delayed latency to convulsion, increased % protection and decreased % convulsion rate when compared with PTZ-treated groups. Meanwhile, DT (61.25 mg/kg, p.o.) failed to protect mice against PTZ-induced convulsion in comparison with PTZ control groups (Table 2).

Table 2: Effect of methanol seed extract of Dennetiatripetala on PTZ-induced convulsions

Group	Dose (mg/kg)	Latency to convulsion (s)	Convulsion (%)	Protection (%)
Control (NS)	10 mL/kg	33.50 ± 3.21	100	0
D. tripetala	61.25	67.83 ± 7.78	80	20
D. tripetala	122.5	78.17 ± 8.76*	60*	40*
D. tripetala	245	90.33 ± 9.15*	0*	100*
Diazepam	2	165.0 ± 16.84*	0*	100*

Each value represents the mean ± S.E.M of 6 animals/group. *$p < 0.05$ as compared with control (vehicle) (one-way ANOVA followed by Bonferroni *post hoc* test). NS = Normal saline

Effect of methanol seed extract of Dennetia tripetala and flumazenil on PTZ-induced convulsion

The effect of flumazenil on the methanol seed extract of *D. tripetala* is shown in Table 3. Administration of methanol seed extract of DT (122.5 mg/kg, p.o.) and DP (2 mg/kg, p.o.) demonstrated marked reduction in PTZ-induced convulsion compared with PTZ control group. However, flumazenil (2 mg/kg, i.p.) pretreatment significantly ($p < 0.05$) suppressed the anticonvulsant-like activity of methanol seed extract of DT (122.5 mg/kg, p.o.) when compared with DT-treated group alone. Similarly, pretreatment with flumazenil (2 mg/kg, i.p.) prior to DP (2 mg/kg, p.o.) treatment significantly ($p < 0.05$) reversed the anticonvulsive-like activity elicited by DP relative to DP-treated group.

DISCUSSION

The results of this study revealed that the LD_{50} of oral administration of methanol seed extract of *D. tripetala* is 2449.48 mg/kg. Pentobarbital-induced sedation and

Table 3: Effect of Dennetia tripetala and flumazenil on PTZ-induced convulsions

Group	Dose (mg/kg)	Convulsion and mortality (%)	Protection (%)
Control (NS)	10 mL/kg	100	0
D. tripetala	122.5	40*	60*
Diazepam	2	0*	100*
Flumazenil (FLU)	2	90	10
D. tripetala + FLU	122.5 + 2	100$^{\#}$	0$^{\#}$
Diazepam+ FLU	2+ 2	100^{a}	0^{a}

Each value represents the mean ± S.E.M of 6 animals/group. *$p < 0.05$ as compared with control; #$p < 0.05$ as compared with DT+FLU; $^{a}p < 0.05$ as compared with DP+FLU (one-way ANOVA followed by Bonferroni *post hoc* test). NS = Normal saline

hypnosis is a popular and well-established preclinical animal model for screening of compounds with suspected sedative and hypnotic activities (Lester et al., 2012; Hamedi et al., 2019). Intraperitoneal injection of pentobarbital induces hypnosis in laboratory animals by binding and activating $GABA_A$ receptor (Hamedi et al., 2019). This results in enhancement of GABA binding and opening of transmembrane chloride channels leading to cellular hyperpolarization within the central nervous system (Hamedi et al., 2019). In this regard, administration of pentobarbital causes enhancement of GABA-mediated inactivation of sensory cortex and reticular activating system thereby leading to dose-dependent muscle relaxation, sedation and hypnosis (Lester et al., 2012; Hamedi et al., 2019). The usefulness of pentobarbital in the assessment of sedative-hypnotic activity is usually based on the ability of test compounds to prolong pentobarbital-induced hypnosis (Rakhshandeh et al., 2012; Hosseini et al., 2014), and this presented decrease in sleep latency and increase in total sleeping time relative to control (Rakhshandeh et al., 2010, 2012; Hosseini et al., 2014). The finding in this study, that methanol seed extract of *D. tripetala* decreased the sleep latency and increased the total sleeping time in pentobarbital-treated mice suggests sedative-hypnotic activity and a beneficial role in conditions associated with behavioral hyperactivity and sleeplessness.

PTZ-induced convulsion has been shown to strongly mimic absence epilepsy and clonic convulsive seizures seen in humans and is known to be sensitive to the inhibitory effect of anticonvulsant drugs(Löscher et al., 1991).Various studies have reported that PTZ induces convulsions by antagonizing GABAergic-mediated postsynaptic inhibitory activity in the central nervous system via competitive blockade $GABA_A$ receptor complex in the temporal lobe and hippocampus (Bolaris et al., 2005; Emoto et al., 2015; Gol et al., 2017).This antagonism of the postsynaptic $GABA_A$ receptor leads to production of discriminative stimulus that causes excessive neuronal excitation, anxiety and convulsion (*Jung et al., 2002;* Gol et al., 2017). In this study, PTZ was found to produce convulsion, which further supports previous investigations showing that PTZ induced convulsive-like behavior in rodents (Löscher et al., 1991; Emoto et al., 2015; Gol et al., 2017). However, anticonvulsant activity in PTZ-induced convulsion is generally based on the ability of test compounds to prevent seizure occurrences by prolonging the latency to convulsion or reduce the duration of convulsion (Rogawski and Porter, 1990; Löscher et al., 1991). It has been observed that test drugs that can delay the occurrence of convulsion might be efficacious in attenuating the spread of seizures in the brains of patients with epilepsy in clinical settings (Löscher et al., 1991; Gol et al., 2017).Thus, the ability of methanol seed extract of *D. tripetala* to significantly prevent PTZ-induced convulsion as evidenced by increased latency to convulsion, % convulsion and protection rates suggests anticonvulsant effect. The involvement of the GABAergic pathway in the anticonvulsant-like activity of *D. tripetala* was studied using flumazenil, a $GABA_A$ receptor antagonist which acts by decreasing GABA binding and opening the transmembrane chloride channels thus leading to increased neuronal excitability and behavioral hyperactivity (*Savic*, 1991; *Danka et al., 2005;* Ayoka et al., 2006).The finding that flumazenil attenuated the anticonvulsant effect of *D. tripetala* suggests that its anticonvulsant-like effect may be mediated via enhancement of central GABAergic neurotransmission.

Anxiety is a common symptom associated with several neuropsychiatric diseases such as epilepsy (Ekeh and Ekrikpo, 2015). PTZ, a prototypical GABA antagonist, induces anxiety largely due to altered $GABA_A$ receptor signaling, and has been extensively used in animal model of anxiety (*Jung et al., 2002*).Hence, in the course of drug discovery of antiepileptics, it is also important to evaluate the anxiolytic property of anticonvulsant agents. The elevated plus maze (EPM) is a popular preclinical paradigm used for the assessment of the anxiolytic effect of test compounds based on the approach-avoidance model (Cryan and Holmes, 2005;

Ben-Azu et al., 2018). The test is centered on the natural tendency of rodents to explore two conflicting environments such as closed arm (approach) and open arm (aversive) (Pellow et al., 1985; Ben-Azu et al., 2018). Previous studies have established that the usefulness of EPM in the assessment of anxiolytic effect of test compounds is based on the increased natural preference of rodents to explore the open arm at the expense of the closed arm (Pellow et al., 1985; Ben-Azu et al., 2018). In this study, our finding showed that methanol seed extract of *D. tripetala* demonstrates anxiolytic activity, as shown by increased duration of time spent and frequency of visitation to the open arm which was also accompanied by corresponding decrease in the duration of time and frequency of visitation to the closed arm in a similar manner to diazepam. To the best of our knowledge, this is the first neuropharmacological report showing the anxiolytic effect of seed extract of *D. tripetala* in mice. However, as part of our ongoing studies on *D. tripetala*, the results of this study are preliminary and thus, require further investigationwith typical disease condition associated with anxiety.

The beneficial effect of *D. tripetala* in this study may be ascribed to the presence of essential oils such as β-phenylnitroethane, β-endesmol, nerolidol, Linalol, β-Caryophyllene and β-Humuline, as well as other bioactive compounds like alkaliodal (uvariopsine, Stephan thrine, argintinine), flavonoids, vitamins (A, C and E) and trace elements (Ekundayo et al., 1992; Adeotiet al., 2000; Elekwa et al., 2011;Oyemitan et al., 2019). Phytochemical analyses of the plant revealed the presence of phenolic rich compounds such as flavonoids, tannins and saponin glycosides, all of which have been reported to possess functional health benefits. In terms of safety and tolerability, *D. tripetala* is generally regarded as safe for human consumption, as it forms a prominent component of our diet as fruit and condiments (Okafor, 1980). Moreover, the LD_{50} (2449.48 mg/kg) of oral administration of methanol seed extract of *D. tripetala* from our study showed that the plant is relatively safe.

CONCLUSION

The results of this study revealed that the seed extract of *Dennettia tripetala* possesses anticonvulsant, hypnotic and anxiolytic properties. The findings that it reduces anxiety-like behaviors and increases sleeping time suggest its usefulness in improving the quality of life of patients with epilepsy. Interaction study with flumazenil suggests that GABAergic pathway may play a role in the anticonvulsant, hypnotic and anxiolytic effects of *D. tripetala.*

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest

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